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(54) PROCESS FOR THE PREPARATION OF ISOUREA HYDROGEN SULPHATES

(71) We, GLAXO LABORATORIES LIMITED, a British Company, of Greenford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention concerns a process for the production of the hydrogen sulphate salts of O - alkyl and O - aralkyl isoureas.

O - Alkyl and O - aralkyl isoureas and their salts are important as synthetic reagents in that they react with amines to produce guanidines and since many guanidines are produced and utilized on a large scale it is desirable that the manufacture of the isourea reagents be as economical as possible. The sulphate salts of the above isoureas have been used in the past for the preparation of guanidines; we have now found that the above isoureas can be satisfactorily employed in the form of their hydrogen sulphate salts as starting materials in this preparation, provided appropriate pH adjustment is made. We have further found conditions under which such hydrogen sulphate salts can be prepared from simple starting materials in greater yield than either the sulphates or hydrogen sulphates previously described.

According to the present invention we provide a process for the preparation of an O-alkyl or O - aralkyl isourea hydrogen sulphate whereby cyanamide is reacted with an alkanol or an aralkyl alcohol in the presence of at least one mole of sulphuric acid relative to the cyanamide.

By including at least one mole of sulphuric acid in the reaction medium, it is possible to ensure that the hydrogen sulphate rather than the sulphate salt of the isourea is produced. The proportion of sulphuric acid is preferably less than 5 moles, conveniently less than 2.5 moles. The most preferred range is 1 to 1.25 moles, for example about 1.125 moles.

The alcohol component is preferably present in the stoichiometric proportion or in excess. Advantageously there are at least 2 equivalents of alcohol present, based on the cyanamide, and while the maximum proportion of alcohol is not critical, the most preferred range is 2 to 10 equivalents, for example about 7. The preferred alcohols are ethanol or, more preferably, methanol, which yield O - ethyl and O - methyl isourea hydrogen sulphate respectively.

The reaction may be effected in the presence or absence of an inert solvent which is miscible with the alcohol reactant, for example a cyclic or acyclic ether solvent, e.g. diethyl ether, di - isopropyl ether, tetrahydrofuran or dioxan; a lower ketone, for example acetone, methylethyl ketone or cyclohexanone; a nitrile solvent, for example acetonitrile or propionitrile; an ester solvent, for example methyl or methyl acetate; a hydrocarbon solvent such as benzene, toluene, hexane or heptane; or a halogenated hydrocarbon solvent such as chloroform, methylene chloride or carbon tetrachloride. It is preferred, however, to carry out the reaction in solution in an excess of the alcohol reactant, in the absence of an added inert solvent.

The reaction is preferably carried out at a relatively low temperature, for example −10° to 20°C, preferably 5—15°C. It will be appreciated that the admixture of the sulphuric acid and the alkanol or aralkanol will give off a great deal of heat and that cooling will be required. The reaction of the cyanamide with the mixture of sulphuric acid and the alkanol or aralkanol is also exothermic. It is preferred, therefore to mix the sulphuric acid with a major proportion of the alkanol or aralkanol with cooling in the initial stage and to cool this mixture prior to reaction with the cyanamide. The latter is advantageously also in solution, either in a proportion of the alcohol reactant or in an inert solvent of the type described above. In order to allow heat to be dissipated, it is preferable to add the solution of sulphuric acid in the alcohol, slowly with stirring and, if

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necessary, cooling, to the cyanamide solution. The latter can advantageously be at low temperature, for example 0°—10°C prior to the addition and the temperature is preferably kept low, for example at −5° to +5°C, during the addition stage. The reaction may then be allowed to proceed to completion at a higher temperature e.g. about 5—15°C.

It is particularly convenient that the desired hydrogen sulphate can be caused to precipitate in very high yield and in excellent purity, simply by addition of a non-polar solvent which is miscible with the alcohol reactant. This non-polar solvent may be one of those set out above as possible inert solvents. The best results have been obtained with aliphatic ethers, especially diethyl ether, with cyclic ether solvents, especially tetrahydrofuran and with lower alkyl ketones such as acetone and methyl ethyl ketone. The volume of precipitating solvent required will vary with the solubility of the desired hydrogen sulphate in the reaction medium. Where an inert solvent is already present, comparatively little precipitating solvent will be required.

However, the desired product may be isolated simply by evaporating off the solvent and although the product may be in a non-crystalline condition, it can normally be used directly in a reaction with an amine to give a guanidine after suitable pH adjustment.

The formation of guanidines using isourea hydrogen sulphates may be effected by admixing the appropriate amine with the hydrogen sulphate, the pH of reaction being adjusted to about 7—9, preferably about 8.5, e.g. by addition of a base such as an alkali metal hydroxide or carbonate. The preferred reaction medium is water.

The amine used is advantageously 1,17-diamino - 9 - azaheptadecane, whereby the compound 1,17 - diguanidino - 9 - azaheptadecane sesquisulphate may be isolated. This compound is particularly useful in seed dressings by virtue of its antifungal activity and low solubility in water (5% or less).

The method according to the invention produces the hydrogen sulphate salt of the desired isourea in high yield. Where other salts are required, these can be prepared from the hydrogen sulphate by anion exchange, for example using anion exchange resins or metathesis. As indicated above, the hydrogen sulphate can be used, in reactions where the sulphate is normally required, by adjustment of the pH.

For the better understanding of the invention the following Examples are given by way of illustration only: all temperatures are in °C:—

Example 1

Concentrated sulphuric acid (0.72 l. 13.5 mole) was added slowly with stirring and cooling to methanol (1.5 l.). This mixture was then added to a cooled, stirred solution of cyanamide (500 g. 11.9 mole) in methanol (1.0 l.). The temperature was kept between −5° and +5° (occasionally rising to 10°), the addition requiring 2.5 hours. The mixture was stirred at 10° for a further hour. Ether (5 l.) was added with stirring and the crystalline product collected by filtration and washed with 20% methanol/ether (2.5 l.). After drying *in vacuo* at 40°, O-methylisourea hydrogen sulphate was obtained in 84.5% yield (1.733 kg.) m.p. 118—120°.

Example 2

Concentrated sulphuric acid (6.81 ml., 0.128 mole) was dissolved in methanol (13.62 ml.) with stirring at less than 5°. The solution was then added carefully to a solution of cyanamide (4.56 g., 0.108 mole) in methanol (9 ml.) with stirring and cooling. The mixture was stirred at 10° for 1 hour, the methanol removed under reduced pressure and the solid O-methyl isourea hydrogen sulphate residue dissolved in water (162 ml.). The pH was adjusted to 8.5 with 10% aqueous sodium hydroxide (58 ml.) and 1,17-diamino-9 - azaheptadecane (10.84 g. 0.04 mole) added, the mixture was stirred for 22 hours at 42°, cooled, and the pH of the suspension adjusted to 2.4 by the addition of 3.2 N sulphuric acid (16.2 ml.). The resulting solution was clarified by filtration through kieselguhr and concentrated to 50 ml. under reduced pressure. The suspension was set aside at room temperature overnight. The product was filtered off, washed with 40:60 aqueous Industrial Methylated Spirits (IMS), with IMS and dried *in vacuo* at 40°. It was then rewashed with water (50 ml.), aqueous IMS and IMS and dried *in vacuo* at 40° to give 14.55 g. (75.6% theory) of 1,17 - diguanidino - 9 - azaheptadecane sesquisulphate of melting range 230—247°.

Example 3

Concentrated sulphuric acid (12.9 ml., 0.25 mole) was dissolved in absolute ethanol (60 ml.) with stirring and cooling. Cyanamide (10.5 g., 0.25 moles) in absolute ethanol (40 ml.) was treated with the acid solution at below 5° with stirring. The solution was stirred for 1 hour at 10°. The ethanol was stripped off under reduced pressure to give 37.24 g. of O - ethyl isourea hydrogen sulphate gum which was dissolved in water (405 ml.). 10% Sodium hydroxide (73 ml.) was used to adjust the pH to 8.5 and the total volume made up to 542 ml. with water. 1,17 - diamino - 9 - azaheptadecane (27.15 g., 0.1 mole) was added and the mixture stirred at 43° for 22 hours, cooled to room temperature and the pH adjusted to 2.4 by the addition of 3.2 N sulphuric acid (50 ml.).

The solution was filtered through kieselguhr, concentrated to 140 ml. under reduced pressure and left overnight to crystallise. The product was collected by filtration, washed with 40:60 aqueous IMS and IMS, then dried *in vacuo* at 40° to give 44.5 g. (89%) of 1,17 - diguanidino - 9 - azaheptadecane sesquisulphate of melting range 219—245°.

Example 4

Effect of a variety of solvents on the precipitation of O - methylisourea hydrogen sulphate from the reaction mixture

A solution of cyanamide (5.0 g.) in methanol (10 ml.), concentrated sulphuric acid (7.2 ml.) in methanol (15 ml.) was added with stirring and cooling to maintain the temp. between 10 and 15°. The mixture was then stirred another hour—the temp. rose to 25° at one time but was rapidly restored to 15° by appropriate cooling. Some of the product crystallised from the reaction mixture. Samples of the supernatant liquid were withdrawn and treated with a variety of solvents. The results are shown in the following table:

TABLE

Tetrahydrofuran	+++
Dioxan	+
Isopropyl ether	+
Ethylacetate	++
Chloroform	+
Dichloromethane	+
Acetone	+++
Methylethyl ketone	+++
Cyclohexanone	+
Acetonitrile	+++

Code:
+++ good separation of crystals
++ Crystals and gum rapidly solidifying
+ gum, slowly crystallising on scratching

WHAT WE CLAIM IS:—

1. A process for the preparation of an O - alkyl or O - aralkyl isourea hydrogen sulphate wherein cyanamide is reacted with an alkanol or an aralkyl alcohol in the presence of at least one mole of sulphuric acid relative to the cyanamide.

2. A process as claimed in claim 1 wherein the reaction is effected in the presence of less than 5 moles of sulphuric acid.

3. A process as claimed in claim 2 wherein the reaction is effected in the presence of less than 2.5 moles of sulphuric acid.

4. A process as claimed in claim 3 wherein the reaction is effected in the presence of from 1 to 1.25 moles of sulphuric acid.

5. A process as claimed in any of the preceding claims wherein the alcohol component is present in the stoichiometric proportion or in excess.

6. A process as claimed in claim 5 wherein at least 2 equivalents, based on the cyanamide, of the alcohol component are present.

7. A process as claimed in claim 6 wherein from 2 to 10 equivalents of the alcohol component are present.

8. A process as claimed in claim 7 wherein about 7 equivalents of the alcohol component are present.

9. A process as claimed in any of the preceding claims wherein the alcohol component is ethanol or methanol.

10. A process as claimed in any of the preceding claims wherein the reaction is effected in the presence of an inert solvent which is miscible with the alcohol reactant.

11. A process as claimed in claim 10 wherein the solvent comprises a cyclic or acyclic ether, a ketone with 3 to 6 carbon atoms, a nitrile, an ester, a hydrocarbon or a halogenated hydrocarbon.

12. A process as claimed in claim 11 wherein the solvent comprises diethyl ether, di-isopropyl ether, tetrahydrofuran, dioxan, acetone, methyl ethyl ketone, cyclohexanone, acetonitrile, propionitrile, methyl or ethyl acetate, benzene, toluene, hexane, heptane, chloroform, methylene chloride or carbon tetrachloride.

13. A process as claimed in any of the preceding claims wherein the reaction is effected at a temperature of from −10° to 20°C.

14. A process as claimed in claim 13 wherein the reaction is effected at a temperature of from 5 to 15°C.

15. A process as claimed in any of the preceding claims wherein the sulphuric acid is first mixed with a major proportion of the alkanol or aralkanol with cooling and this mixture is cooled prior to reaction with the cyanamide.

16. A process as claimed in any of the preceding claims wherein the cyanamide is in the form of a solution in a proportion of the alcohol reactant or an inert solvent.

17. A process as claimed in claim 16 wherein a solution of sulphuric acid in alcohol is added to the cyanamide solution slowly with stirring.

18. A process as claimed in any of claims 15 to 17 wherein the admixture of the sulphuric acid and alcohol with the cyanamide is effected at a low temperature.

19. A process as claimed in claim 18 wherein the temperature is from −5° to +5°C.

20. A process as claimed in any of the preceding claims wherein the desired hydrogen sulphate is precipitated by addition of a non-polar solvent which is miscible with the alcohol reactant.

21. A process as claimed in claim 20

wherein the non-polar solvent comprises an aliphatic or cyclic ether or an alkyl ketone with 3 to 6 carbon atoms.

22. A process as claimed in claim 21 wherein the non-polar solvent comprises diethyl ether, tetrahydrofuran, acetone or methyl ethyl ketone.

23. A process as claimed in any of the preceding claims wherein the hydrogen sulphate obtained is subsequently converted to another salt by anion exchange.

24. A process as claimed in claim 1 substantially as herein described.

25. A process as claimed in claim 1 substantially as herein described in any of the Examples.

26. O - alkyl and O - aralkyl isourea hydrogen sulphates when prepared by a process as claimed in any of the preceding claim.

27. A process as claimed in any of claims 1 to 25 wherein, for the preparation of guanidines, an O - alkyl or O - aralkyl isourea hydrogen sulphate first prepared is subsequently admixed with the appropriate amine, the pH being adjusted to about 7 to 9.

28. A process as claimed in claim 27 wherein the pH is adjusted to about 8.5.

29. A process as claimed in claim 27 or claim 28 wherein the pH is adjusted by addition of an alkali metal hydroxide or carbonate.

30. A process as claimed in any of claims 27 to 29 wherein the reaction is effected in the presence of water.

31. A process as claimed in any of claims 27 to 30 wherein the amine used is 1,17-diamino - 9 - azaheptadecane.

32. A process as claimed in claim 27 substantially as herein described.

33. A process as claimed in claim 27 substantially as herein described in Example 2 or Example 3.

34. Guanidines when prepared by a process as claimed in any of claims 27 to 33.

35. 1,17 - diguanidino - 9 - azaheptadecane sesquisulphate when prepared by a process as claimed in claim 31.

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